

MODERATE-VIGOROUS PHYSICAL ACTIVITY AND CLINICAL PARAMETERS IN ADULTS WITH TYPE 2 DIABETES MELLITUS: A REPORT FROM THE WALKING WITH DIABETES STUDY

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Abstract

Background and aims: This study investigate the effects of increases in moderate-vigorous physical activity (MVPA) on several clinical parameters in Indonesian type 2 diabetes mellitus (T2DM) patients. **Material and methods:** This study used clinical and physical activity data of forty-two T2DM patients who completed a 6 month-free-living physical activity program, the Walking with Diabetes Study. Upon completion of the program, participants were categorised into a group with increases in MVPA (the MVPA+ group, n=24) or a group with steady/decreases in MVPA (the control group, n=18). High density lipoprotein, triglyceride, routine hematology profiles, blood pressure, body mass index, weight/hip ratio and self-reported MVPA, at baseline, 3 and 6 months were retrospectively analysed. Generalized estimating equation adjusted for age and sex were conducted to assess group and time effects on the clinical parameters. **Results:** Hemoglobin ($p < 0.01$), erythrocytes ($p < 0.05$), hematocrits ($p < 0.001$) and thrombocytes ($p < 0.05$) were higher in the MVPA+ group. The 1h and 2h-erythrocyte sedimentation rate (ESR) increased in both groups across time ($p < 0.001$). No changes between groups across time were found for other parameters. **Conclusions:** Increases in MVPA improve several hematology parameters in T2DM patients, but it does not have protective effects in controlling systemic inflammation in T2DM patients.

key words: physical activity, haematology, lipids, blood pressure, body weights and measures

Background and aims

Indonesia, like many countries worldwide, is facing a rapid increase in type 2 diabetes mellitus (T2DM) cases, which causes a significant public health burden [1,2]. The burden is mostly associated with enormous health expenditure and resources required for managing T2DM complications [3,4]. Since

physical activity has significant roles in managing T2DM and preventing T2DM complications, physical activity remains a cornerstone of T2DM management [5].

Insulin resistance which is the core aetiology of the T2DM is not only disruptive to the glucose hemostasis but is also associated with abnormalities of plasma lipid and lipoprotein (dyslipidemia) [6]. Dyslipidemia increases the

risk of cardiovascular diseases in T2DM patients [7], thus, addressing dyslipidemia is one of the goals of T2DM management. Evidence has shown that supervised exercise improves dyslipidemia in T2DM [8], however, the role of free-living physical activity program in improving dyslipidemia is still inconclusive. Further research, therefore, is required to investigate the role of free-living physical activity program in improving lipid profiles among T2DM patients.

T2DM mostly affects older people, who are susceptible to experience down-regulation on hematologic and immunological functions [9,10]. Studies have showed that resistive endurance exercises alter these changes by improving haemoglobin, erythrocytes, hematocrit and leucocytes in healthy older adults [10]. However, the effect of free-living physical activity improvement in T2DM patients' haematology profile, have not been investigated. The other T2DM comorbidities are hypertension, overweight and obesity, which also increase the risk of T2DM complications [11]. Supervised exercise sessions have found to improve blood vessel elasticity and autonomic nerves imbalances, therefore, improves blood pressure [12]. Physical activity also increases energy expenditure creating negative net energy for losing weight. However, further research is required to investigate the effect of free-living physical activity program on improving these conditions in T2DM populations.

Walking with Diabetes (WW-DIAB study) was a study recently conducted in Indonesian T2DM population which mainly aimed to explore the effectiveness of a free-living physical activity intervention in improving physical activity levels, glycaemic control, social cognitive measures and health-related quality of life in an Indonesian T2DM [13]. The study reveals that the program increases walking

activity, self-reported moderate-vigorous physical activity (MVPA) and glycemic control, in most of their study population. However, the effects of the MVPA increases on the lipid profiles, hematology profiles, anthropometric measures and blood pressure in that population have not been discussed. This study aimed to explore the effect of the MVPA increases on those clinical parameters.

Material and methods

Ethical statements

This study was approved by the Ethics Committee of the Queensland University of Technology, with approval number 1500000562. Participants' personal information was collected, shared, and maintained to protect confidentiality before, during, and after the trial. All participants were fully informed and provided with written informed consent

Study Design, Sample Size and Study population

This study is a retrospective longitudinal study of a cohort of T2DM patients who completed a 6-month physical activity program, the Walking with Diabetes Program [13]. The program aimed to support Indonesian T2DM to increase their physical activity levels. From 43 participants, 42 (98%) completed the program; therefore, they included in this current study. The participants were T2DM patients regularly attending a diabetes clinic and or the T2DM exercise program at a local public hospital in Yogyakarta, Indonesia.

Study outcomes

Upon completion of the walking program, participants were grouped based on their MVPA status, compared to their baseline MVPA levels. The first group was the group experiencing increases in MVPA levels at the end of the

program (the MVPA+ group) while the second group was the group with steady/decreases in their self-reported MVPA at the end of the program (the control group). The clinical outcome that were analysed included (1) lipid profile (i.e., high density of lipoprotein (HDL) and triglyceride), (2) complete hematology profile (i.e. hemoglobin, erythrocytes, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular haemoglobin concentration red cell width distribution, thrombocytes, leukocytes, lymphocytes, monocytes, neutrophil, eosinophil, basophil, first-hour erythrocytes sedimentation rate (ESR) and second-hour ESR, (3) blood pressure parameter (systole and diastole) and (4) anthropometric measures (body mass index and waist/hip ratio).

Data collection, data adherence, data management and data quality assurance

This study utilised clinical parameters and physical activity data from the WW-DIAB Study. In the WW-DIAB study, the data collection were conducted with the support of two phlebotomists and one laboratory technician in a private clinical laboratory in Yogyakarta at baseline, 3 and 6 months. For lipid and haematology profile assessment, participants' blood was drawn by a phlebotomist. The self-reported MVPA data was collected using 7-day physical activity recall, conducted by the lead author. The blood pressure and anthropometric measures were conducted by research assistants. The data were double checked for ensuring the accuracy of the data. The range checks for data values were conducted and validated before the data were imported into a statistical program for analysis. Methods for assessing those outcomes and the corresponding normal reference range values are available in [Table 1](#).

Table 1. Study outcomes, instruments, and normal reference range.

Study Outcomes	Methods/Formula	Normal Reference Range
Lipid profile		
High density lipoprotein	Homogeneous methods	Male >40 mg/dl Female >50 mg/dl
Triglyceride	Glycerol phosphate oxidase	<150 mg/dl
Haematology Parameters		
Haemoglobin	Sulfolyser Haemoglobin	Male: 13.2-17.3 gr/dl Female: 11.7-15.5 gr/dl
Erythrocytes	Hydrodynamic focussing	Male: 4.4-5.9 million/uL Female: 3.8-5.2 million/uL
Haematocrit	Hydrodynamic focussing	Male: 40-52% Female: 35-47%
Mean corpuscular volume	Hydrodynamic focussing	80-100 fl
Mean corpuscular haemoglobin	Hydrodynamic focussing	26 – 34 pg
Mean corpuscular haemoglobin concentration	Hydrodynamic focussing	32 – 36 g/dl
Red blood cell distribution width	Hydrodynamic focussing	11.5 -14.5
Thrombocytes	Hydrodynamic focussing	150-440 thousand/uL
Leucocytes	Flowcytometry laser semiconductor	Male: 3.8-10.6 thousand/L Female: 3.6 -11 10 thousand/L
Lymphocytes	Flowcytometry laser semiconductor	25-40%
Monocytes	Flowcytometry laser semiconductor	2-8%
Neutrophil	Flowcytometry laser semiconductor	50-70%
Eosinophil	Flowcytometry laser semiconductor	2-4%
Basophil	Flowcytometry laser semiconductor	0-1%

Table 1. *Continued.*

Study Outcomes	Methods/Formula	Normal Reference Range
1 and 2-hour Erythrocytes Sedimentation Rate	Infrared sensor method with Westergreen value presentation	Male: 0-10 mm/hr Female: 0-20 mm/hr
Blood Pressure		
Systole	Sphygmomanometer	<130 mmHg
Diastole	Sphygmomanometer	<90 mmHg
Anthropometry status		
Body mass index	(Weight (kg)) ² /Height (m)	<23.5 kg/m ²
Waist/hip ratio	Waist/Hip circumference	Female <0.8 Male < 0.9

Analysis plan (statistical analysis)

For descriptive purposes, at baseline, the social demography and clinical outcome data were compared between the MVPA+ and the control group. The data were summarized using means and standard deviation for continuous data and proportions for ordinal and nominal data. The longitudinal analyses were conducted using generalized estimating equation models (GEE) to plot the clinical outcomes data by group (MVPA+ or control groups), time (baseline, 3 and 6 months), and group by time interactions. The clinical outcomes and physical activity levels could be influenced by age and sex; thus, these can be potential confounders, thus, the analyses were adjusted for age and sex.

The GEE method of analysis was selected because the main interest is the average changes in the health outcomes across time. The physical activity and clinical outcome data were also non-normally distributed, thus best accommodated

with GEE methods. The covariance structure that generated the smallest ‘quasi-likelihood under the independence model criterion’ (QIC) was selected for predicting each outcome for the GEE modelling. Prior to the main data analysis, a MCAR (missing completely at random) statistical analysis was carried out to ensure that the data meet the assumptions of the GEE analysis. All of the analyses were conducted in SPSS 22.

Results

Participants Characteristics and Clinical Parameters at Baseline Comparisons

The detailed comparisons of social demography and clinical parameters in the MPVA+ and the control group at baseline are presented in [Table 2](#).

Table 2. The comparison of social demography and clinical parameters at baseline.

Variables	Control group (n=18)	MVPA+ group (n=24)	p-value
Age (years): mean ±SD	66.4±7.4	64.7±4.6	0.016
Sex: n (%)			
Women	10 (56 %)	16 (67 %)	0.531
Men	8 (44 %)	8 (33 %)	0.506
Marital status: n (%)			
Married	14 (78%)	16 (67%)	0.506
Not married	4 (22%)	8 (33%)	

Table 2. Continued.

Variables	Control group (n=18)	MVPA+ group (n=24)	p-value
Education level: n (%)			
Up to high school diploma	9 (50%)	16 (67%)	0.348
Diploma or higher	9 (5%)	8 (33%)	
Employment status: n (%)			
Paid work	2 (11%)	5 (21%)	0.564
No paid work	5 (28%)	8 (33%)	
Retired	11 (61%)	11 (46 %)	
Smoking status: n (%)			
Smoker	0 (0 %)	1 (4%)	0.658
Non-smoker	16 (89%)	21 (88%)	
Ex-smoker	2 (11%)	2 (8%)	
T2DM duration (years): n (%)			
<5	3 (17%)	3 (12%)	0.812
5-10	8 (44%)	11 (46%)	
>10	7 (39%)	10 (42%)	
Treatment status: n (%)			
Oral	15 (83%)	24 (100 %)	0.071
Insulin	3 (17%)	0 (0%)	
Anthropometry status			
Body mass index	25.2±4.1	24.7±2.9	0.930
Waist/Hip ratio	0.89±0.06	0.90±0.05	0.405
Blood pressure parameters			
Systole	127±13	124±11	0.559
Diastole	78±6	76±6	0.373
Lipid Parameters			
HDL	51±13	48±8	0.067
Triglyceride	122±56	130±81	0.392
Haematology parameters			
Haemoglobin	13.2±1.2	13.7±1.3	0.760
Erythrocytes	4.57±0.53	4.72±0.45	0.359
Haematocrit	0.39±0.03	0.41±0.04	0.307
Mean corpuscular volume	87±8.9	87±4.2	0.05
Mean corpuscular haemoglobin	29.2±3	29.3±1.5	0.039
Mean corpuscular haemoglobin concentration	335±13	335±8	0.096
Red blood cell distribution width	0.14±0.01	0.13±0.01	0.124
Thrombocytes	232±58	274±60	0.800
Leucocytes	7.8±3	7.2±1	0.000
Lymphocytes	30±9	31±8	0.707
Monocytes	7±2	7±1	0.802

Table 2. Continued.

Variables	Control group (n=18)	MVPA+ group (n=24)	p-value
Neutrophil	60±11	59±8	0.24
Eosinophil	3±2	3±2	0.652
Basophil	0	0	-
1-hour ESR	13±9	16±12	0.445
2-hour ESR	27±17	35±24	0.369

There were no differences at social demography characteristics between the two groups except for age. Participants in the MVPA+ group were younger than the control group (64±5 compared to 66±7 years, $p<0.05$). Most participants in both groups have been diagnosed with T2DM for more than 5 years and received oral antidiabetic medication. Three participants (17%) in the control group, however, took insulin daily, while none was participants in the MVPA group ($p=0.07$). At baseline, no difference between groups was found on all the anthropometric measures, blood pressure parameters and lipid profiles, as well as on all routine hematology parameters except for the mean corpuscular volume and leucocytes count. Higher mean corpuscular hemoglobin ($p=0.04$) and lower of leucocytes count ($p<0.001$) were found in the MVPA+ group, at a baseline. The values in both groups, however, were still within the normal reference values.

Moderate and Vigorous Physical Activity Improvement during the WW-DIAB program

At baseline, only 6 (33%) of the control group participants and 3 (12.5%) of the MVPA+ participants achieved the recommended 150 minutes of MVPA per week ($p=0.14$). Their baseline MVPA minutes/week for the control and MVPA+ groups were 100±78 and 90±72 minutes/week, respectively ($p=0.16$). At the end of the 6-month program, the proportion of

participants in the control group meeting the recommended MVPA times unchanged, while it increased to 18 (75%) ($p=0.01$) in the MVPA+ group. The MVPA times in the control group decreased to 73±71 minutes/week, while it increased to 260±140 minutes per week in the MVPA+ group ($p=0.001$).

Longitudinal Analysis of the Clinical Outcomes (adjusted for age and sex)

[Table 3](#) indicates that there was no group, time and group by time effect found for both HDL and triglyceride across the study period in both groups. There was also no group and group x time effect found for the mean corpuscular hemoglobin, red cell distribution width, leucocytes count and leucocytes sub-population profiles. Participants in the MVPA+ group, however, had higher hemoglobin level, erythrocyte count, hematocrit and thrombocytes count compared to participants in the control group. Lastly, participants in both groups increased the mean corpuscular volume, mean corpuscular hemoglobin concentration, 1 and 2 hour-erythrocyte sedimentation rates, across time ($p<0.001$). There was also no group, group x time and time effect found for diastolic and systolic blood pressure as well as for body mass index and waist/hip ratio.

Table 3. Mean predicted values [95%CI] of the clinical parameters and the model effects adjusted for age and sex.

	Control (n=18)			MVPA+ (n=24)			Model Effects		
	Baseline	3rd month	6th month	Baseline	3rd month	6th month	Group	Time	Group*Time
Lipid Profile									
High density of lipoprotein	51 [46, 57]	53[47, 58]	47 [42, 52]	48 [45, 52]	49 [46, 53]	49 [45, 53]	0.701	0.157	0.138
Triglyceride	122 [97, 148]	114 [95, 139]	140 [116, 164]	129[98, 161]	122 [100, 144]	121 [101, 142]	0.947	0.214	0.150
Haematology Profile									
Haemoglobin	13.2[12.7, 13.8]	13.2 [12.7, 13.7]	12.9[12.3,13.5]	13.8[13.3, 14.3]	13.8[13.2, 14.4]	13.8[13.2, 14.5]	<0.001	0.313	0.151
Erythrocytes	4.6 [4.3, 4.8]	4.6 [4.3, 4.8]	4.4 [4.3, 4.6]	4.7 [4.5, 4.9]	4.8 [4.5, 4.9]	4.8 [4.5, 4.9]	0.048	0.361	0.102
Haematocrit	39 [38, 41]	38 [37, 39]	37 [35, 38]	41 [40, 43]	40 [38, 41]	40 [38, 42]	0.001	0.000	0.046
Mean corpuscular volume	87 [83, 91]	84 [80, 88]	84 [80, 88]	87 [86, 89]	84 [82, 85]	84 [82, 86]	0.756	0.000	0.581
Mean corpuscular haemoglobin	29 [28, 31]	29 [28, 31]	29 [28, 31]	29 [29, 30]	29 [29, 30]	29 [29, 30]	0.834	0.867	0.462
Mean corpuscular haemoglobin concentration	335 [330, 341]	349 [343, 355]	350 [343, 356]	335 [332, 339]	348 [344, 352]	347 [344, 351]	0.797	0.000	0.395
Red blood cell distribution width	.14 [.13, .14]	.14 [.13, .14]	.14 [.13, .14]	.13 [.13, 0.14]	.13 [.13, 0.14]	.13 [.13, .14]	0.223	0.943	0.952
Thrombocytes	233 [207, 259]	251 [229, 274]	248 [226, 271]	275 [251, 297]	261 [239, 283]	257 [235, 280]	0.246	0.801	0.026
Leucocytes	7.8 [6.4, 9.1]	7.3 [6.2, 8.4]	7.7 [6.6, 8.7]	7.2 [6.7, 8.7]	7.0 [6.5, 8.7]	7.0 [6.4, 7.7]	0.355	0.346	0.793
Lymphocytes	30 [26, 34]	28 [24, 33]	28 [23, 32]	31 [28, 34]	31 [28, 34]	31 [28, 34]	0.295	0.615	0.507
Monocytes	7 [6, 8]	6 [6, 7]	7 [6, 7]	7 [7, 8]	7 [6, 8]	7 [6, 8]	0.093	0.514	0.611
Neutrophil	60 [55, 65]	62 [57, 67]	62 [58, 67]	59 [56, 62]	58 [55, 62]	58 [55, 62]	0.192	0.839	0.485
Eosinophil	3 [2, 4]	3 [2, 4]	3 [2, 4]	3 [2, 4]	4 [3, 5]	3 [2, 4]	0.776	0.610	0.764
Basophil	-	-	-	-	-	-	-	-	-
1-hour Erythrocyte sedimentation rate	13 [9, 17]	25 [18, 32]	24 [15, 34]	16 [11, 21]	29 [22, 36]	29 [21, 38]	0.492	0.000	0.934
2-hour Erythrocyte sedimentation rate	27 [19, 35]	49 [37, 61]	42 [29, 55]	35 [25, 44]	58 [47, 69]	50 [40, 59]	0.375	0.000	0.970
Blood Pressure									
Systole	127 [121, 133]	123 [119, 126]	127 [122, 132]	124 [120, 129]	125 [120, 129]	127 [124, 130]	0.782	0.163	0.353
Diastole	78 [73,78]	77 [75, 80]	78 [76, 81]	76 [73, 78]	76 [74, 78]	78 [76, 80]	0.332	0.282	0.414
Anthropometric Parameter									
Body Mass Index	25.2 [23.4, 27.1]	25.3 [23.6, 27.1]	25.4 [23.7, 27.2]	24.7 [23.5, 25.8]	24.6 [23.4, 25.8]	24.4 [23, 25.7]	0.377	0.916	0.388
Waist/Hip Ratio	0.89 [0.86, 0.92]	0.89 [0.87, 0.90]	0.89 [0.87, 0.91]	0.90 [0.88, 0.92]	0.88 [0.87, 0.90]	0.89 [0.87, 0.91]	0.690	0.113	0.657

Discussion

This study explored the effect of moderate-vigorous physical activity (MVPA) increases on high-density lipoprotein, triglyceride, routine haematology profiles, anthropometric measures, and blood pressure parameters in an Indonesian T2DM population. The results of this study show a non-effect of the MVPA increases on the lipid profiles, anthropometric measures and blood pressure. However, those with increases in their

self-reported MVPA times per week (the MVPA+ group), improve several haematology parameters. The improvements, nonetheless, may not be clinically meaningful, since the values were still within the normal reference ranges. The only clinically meaningful findings are the increases of the 1 and 2 hour-erythrocyte sedimentation rates (ESRs) in both groups. It shows that systemic inflammations may have worsened in all participants regardless of their

MVPA status, throughout the 6-month physical activity program.

Since the ESR is a nonspecific inflammation marker, no specific conclusion or diagnosis can be drawn from this increase. The increases could be due to infections, liver and renal disorders, anaemia or neoplasms [14]. Further physical and laboratory examinations are required to rule out these conditions, although, participants in this study did not report symptoms related to these conditions. It is also recommended to explore and confirm the finding using other chronic inflammation parameters such as chronic reactive protein (CRP) and interleukin 6 (IL-6). It is essential since these parameters carry prognostic values in predicting the occurrence of impending T2DM debilitating complications such as nephropathy and retinopathy [15,16].

The ESRs increases in this study were not expected, particularly in light of the improvement of glycemic control (A1C reduction) reported in this population throughout the study period [13], since the ESRs are positively associated with A1C levels. The ESR increases were also unexpected because this study shows physical activity improvement which usually improves systemic inflammations [17,18]. Those previous studies, however, were conducted in non-diabetic populations. The discrepancy is possibly because the chronic adaptation of long-term physical activity improvements well as inflammation regulation in T2DM population is more complex compared to what occurs in non-diabetic populations.

The ESRs increases in this study possibly due to the natural progression of the T2DM and due to the ageing process, because, older individuals tend to have higher ESR values [19]. However, further studies are required to confirm whether 3- and 6-month time differences in older adults could contribute to such increases. In addition, the ESR increase may have only

occurred in selected individuals, thus the characteristics of T2DM patients who are more likely to experience worsening systematic inflammation during a physical activity program need to be explored.

The lack of effect of the increases of MVPA times in improving HDL and triglyceride were in agreement with finding from the Early ACTID study [20]. However, it is in discrepancy with a positive effect reported from a 12-week walking study in T2DM female population in a Nordic Walking program in Norway [21]. The difference of the finding may be attributed to the participants' characteristic differences since the Nordic Walking program only recruited women and that most of their participants were obese ($BMI > 30 \text{ kg/m}^2$) at baseline. Participants in the Nordic walking program may benefit the walking program more than the current study participants who were relatively leaner.

The non-effect of this walking program on the blood pressure parameters is similar to findings from other studies such as the Early Activity in Diabetes Program [20], and the Healthy Eating and Active Living for Diabetes Program [22]. However, the non-effect of the program in improving blood pressure indicators differs from several other studies. Blood pressure improvements have been reported occur in T2DM patients that improved their walking volume and intensity [23]. Similarly, blood pressure improvements were also found in T2DM patients receiving either cognitive behavioural group support to increase walking activity or those who did not [24]. Their participants' baseline systolic pressure, though, was relatively high, at $148.6 \pm 21.0 \text{ mmHg}$ in the control group, and $155.1 \pm 25.3 \text{ mmHg}$ in the intervention group. The lack of effect in blood pressure parameter in this study, therefore, may be because the study participants already had

relatively normal systole and diastole readings at baseline causing a floor effect.

The lack of effect of the MVPA improvements on the BMI was also in line with the finding from the First Step Program (FSP) which studied middle-aged, overweight, and sedentary T2DM patients [25]. However, unlike this study, participants in the FSP study decreased their waist circumference over time [25]. The lack of effect on the BMI and waist and hip ratio in this study was also in discrepancy with several other studies [23,24]. Apart from the differences in the PA level improvements in these studies, these discrepancies may reflect differences in assessment times, physical activity program structures and participant initial weight or BMI.

Strengths and limitations of the study and directions for future research

This study is the first retrospective longitudinal physical activity study in T2DM patients that explores the effect of the MVPA increases on the lipid profiles, haematology profiles, anthropometry and blood pressure parameters. However, two major limitations need to be acknowledged. First, the study recruited all participants who completed the WW-DIAB program, thus, followed the WW-DIAB sample calculation. Therefore, the sample size for this current study might not have sufficiently powered to detect changes in the clinical parameters. Second, there was an age difference between groups, in which the MVPA+ group were found to be younger than the control group. Thus, the clinical parameter response differences in the MVPA+ group may be attributed to this age difference, although, an effort to control the analyses with age has been made. For future research, intervention studies

using a randomised control design could address the problems. Future research also needs to consider the use of other inflammation markers such as CRP and IL-6 which have better prognostic values on major T2DM complications. Lastly, studies to assess and address the impact of the systemic inflammations to prevent T2DM complications are recommended.

Conclusions

The MVPA increases during the 6-month free-living physical activity program do not affect the high density of lipoprotein, triglyceride, blood pressure, and anthropometric parameters in T2DM population. The MVPA increases improved hemoglobin, hematocrit, erythrocyte and thrombocytes, although the improvement may not be clinically significant. The MVPA improvement, however, do not improve the systematic inflammations, which tend to worsen over time regardless their MVPA levels.

Conflict of Interest. There is no conflict of interest.

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